REMARKS

I. The Subject Matter of the Claims

In general, the subject matter of the claims relates to pharmaceutical compositions comprising recombinant human *N*-acetylgalactosamine-4-sulfatase (ASB).

II. Patentability Argument

A. The Rejection of Claims 33-41 Under 35 U.S.C. §112, First Paragraph, Should Properly Be Withdrawn

The Examiner rejects claims 33-41 under 35 USC §112, first paragraph, asserting that the disclosure does not describe all species, mutants and variants of recombinant ASB contemplated by the invention and contends that the claims are drawn to a genus of polypeptides having any structure, which are not described or enabled.

Solely to expedite prosecution, Applicants have amended the claims to recite a recombinant human ASB, thus addressing the Examiner's concern that the claims include ASB from other mammalian species. Applicants respectfully submit that the remainder of the Examiner's rejection with respect to mutants and variants of recombinant ASB is based on a misunderstanding of Applicants claims as originally filed and as presented in the preliminary amendment.

The usage of the term "N-acetylgalactosamine-4-sulfatase" in the specification and original claims makes clear that this term is different from the terms "biologically active fragment, mutant or analog". Claims 33-34 are based on original claims 8 and 14 as filed, which recited "A pharmaceutical composition comprising recombinant N-acetylgalactosamine-4-sulfatase and a pharmaceutically acceptable carrier." Compare this language to that of original claim 22, which recited "recombinant N-acetylgalactosamine-4-

sulfatase enzyme or a biologically active fragment, analog or mutant thereof."

Moreover, the usage of the term "sulfatase" in the specification differentiates between recombinant *N*-acetylgalactosamine-4-sulfatase enzyme and "a biologically active fragment, mutant or analog thereof." For example, page 4, line 33, to page 5, line 35, of the specification describes multiple embodiments of the invention, including a pharmaceutical composition comprising "recombinant *N*-acetylgalactosamine-4-sulfatase(ASB) , or a biologically active fragment, mutant or analog thereof" (page 4, lines 33-35), and methods for producing, methods for administering, and vectors and host cells comprising DNA encoding recombinant *N*-acetylgalactosamine-4-sulfatase, or a biologically active fragment, mutant or analog thereof.

Thus, because the specification and claims as originally filed distinguish between the term "sulfatase enzyme" and the terms "fragment, mutant, or analog," the Examiner is mistaken in asserting that the pending claims include an "extremely large number of ASB [*N*-acetylgalactosamine-4-sulfatase] " (see bottom of p. 4). Applicants note that they respectfully disagree with the Examiner's position that fragments, mutants or analogs lack written description or enablement. Regardless, the description or enablement of such fragments, mutants or analogs simply is not at issue in the pending claims because the claims do not recite fragments, mutants or analogs.

While the claims do encompass naturally occurring human ASBs and the recombinant expression products of DNA encoding human ASB, such as the precursor protein which lacks the signal peptide or other mature forms (see, e.g., the sequence published by Peters et al. (J Biol. Chem. 265:3374-81, 1990), referred to at page 11, line 34,

of the specification), that does not correspond to the "great breadth" or "extremely large number of ASB" of which the Examiner complaints and on which the Examiner's rejection is based.

Applicants submit that because the scope of the claims as filed does not encompass the subject matter the Examiner is rejecting, the rejection of claims 33-41 under 35 U.S.C. §112, first paragraph, is misplaced and should be withdrawn.

B. The Rejection of Claims 33-41 Under 35 U.S.C. §103, Should Properly Be Withdrawn

The Examiner rejects claims 33-41 under 35 USC §103 as assertedly obvious in view of Crawley, which assertedly discloses a recombinant *N*-acetylgalactosamine-4-sulfatase (ASB) and a carrier, in view of Mundorf and Bam, which assertedly disclose use of polyethylenesorbitan 20 or 80, respectively, to stabilize protein compositions.

The Examiner asserts that the composition disclosed in Crawley possesses the properties of the composition claimed in present claim 40. Applicants respectfully disagree.

Crawley discloses recombinant human ASB enzyme preparations having a specific activity of ~25-30,000 mUnits/mg, and which exhibit **two** distinct bands on SDS PAGE. Crawley states that the purified preparations comprise 70% precursor protein and 30% mature protein fragments (p. 1865). In contrast, claim 40 requires that the pharmaceutical composition comprising the rhASB has a much higher specific activity of 40-80,000 mUnits/mg, is 95% pure, and shows only **one** major band of 65-70 kD. Thus, the compositions disclosed by Crawley have different properties than the composition of claim 40. Moreover, Crawley fails to disclose that its compositions have any of the additional

properties specified in claim 40, for example, absence of detectable pathogens, low endotoxin level, low particulate content, or pH in the recited range. Crawley also does not disclose the method by which the ASB was purified. Thus, Crawley does not anticipate claim 40 or claim 41 and the Examiner has not shown how it would be obvious to arrive at Applicants' claimed compositions.

Both Bam and Mundorf indicate that polysorbate is only one of several available agents useful for stabilization of proteins. See Bam page 801, 2nd col., and Mundorf, col. 3, lines 48-61. Both Bam and Mundorf deal with different proteins than ASB, and the Examiner has pointed to no motivation to combine the Crawley reference with either of Bam and Mundorf. In particular, because Mundorf describes use of polysorbate as an emulsifier to make a **topical** solution, a worker of ordinary skill in the art would not combine Mundorf (topical solution) with Crawley (intravenous solution).

Even assuming that it was obvious to try to combine the composition of Crawley with a stabilizing agent of Bam or Mundorf, the Examiner has not shown that there would have been a reasonable expectation of success of making a successful pharmaceutical composition using polysorbate as the stabilizing agent. Not all proteins are stable in polysorbate solution, for example, solubility and aggregation of COX proteins are not improved by the addition of Tween 20 to the solution (Musatov et al., *Biochemistry.* 39:12996-3004, 2000) (submitted herewith). Additionally, inclusion of polysorbate to protein solutions has resulted in precipitation of the protein (Kreilgaard et al., *J Pharm Sci.* 88:281-90, 1999) (submitted herewith) as a result of the polysorbate agent. Based on knowledge in the art at the time, one of ordinary skill in the art would not know whether addition of polysorbate will stabilize or destabilize a protein solution until it is actually

added. Thus, there is no reasonable expectation of success that a person of ordinary skill in the art could use polysorbate as a stabilization agent in a pharmaceutical composition and achieve an active *N*-acetylgalactosamine-4-sulfatase enzyme pharmaceutical solution suitable for administration to a patient.

Because numerous stabilization agents are available for pharmaceutical compositions, and polysorbate can destabilize enzymes or precipitate proteins from solution, a worker of ordinary skill in the art at the effective filing date of the present application would not have been motivated to select polysorbate and moreover would not have a reasonable expectation of success at making an effective pharmaceutical composition comprising the recombinant enzyme ASB in polysorbate. For all of these reasons discussed above, the rejection of claims 33-41 under 35 USC §103 should properly be withdrawn.

C. The Rejections of Claims 33-41 Under The Doctrine of Obviousness-Type Double Patenting May Properly Be Withdrawn

The Examiner provisionally rejected claims 33-41 under the judicially created doctrine of obviousness-type double patenting over the disclosure of co-pending, co-owned U.S.S.N. 10/290,908. Upon allowance of claims 33-41 in the present application, a terminal disclaimer will be filed to moot the Examiner's provisional double patenting rejection.

III. Conclusion

This paper is submitted with a petition for a one month extension of time and a check in the amount of $60 pursuant to 37 CFR 1.17 (a). Please charge any additional fees due in connection with this paper to Marshall, Gerstein and Borun, LLP account number 13-2855.

Applicant's submit that the application is now in condition for allowance and respectfully request notice of the same.

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Respectfully submitted,

By _____

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